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L9: Entry 7 of 17

File: USPT

Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6218122 B1

TITLE: Methods of monitoring disease states and therapies using gene expression profilesDATE FILED (1):
19990616Detailed Description Text (27):5.2. Monitoring Disease States and Therapies from Expression ProfilesDetailed Description Text (74):

In certain embodiments, the methods of the invention can be used to monitor the level of a plurality of disease states simultaneously, or to simultaneously monitor the efficacy of a plurality of therapies. In such embodiments, the perturbation response, $R_{sub.i,k}$ ($P_{sub.i,l}$) of the k 'th cellular constituent at the l 'th perturbation level is separately determined for the i 'th disease state or therapy. The response profiles for each disease are interpolated, as described above, to generate an interpolated response profile for each disease state or therapy, $R_{sub.i,k}$ ($p_{sub.i}$). The diagnostic expression profile D can then be compared to a combination of the perturbation response curves $R_{sub.i}$ ($p_{sub.i}$) for each disease state or therapy to find a best-fit over all possible values of $\{p_{sub.i}\}$. In a particularly preferred embodiment, the effects of therapies and/or the levels of diseases are sufficiently low the nonlinear or feed back effects, discussed above, are not observed. In such an embodiment, the perturbation response profile may simply be compared to the sum of perturbation response curves for each disease, i.e., to $\Sigma R_{sub.i}$ ($p_{sub.i}$). Accordingly, in embodiments where the best fit is determined by minimization of the least squares problem, the best fit is the solution to Equation 5. ##EQU5##

Detailed Description Paragraph Table (1):

TABLE I MALIGNANCIES AND RELATED DISORDERS Leukemia acute leukemia acute lymphocytic leukemia acute myelocytic leukemia myeloblastic promyelocytic myelomonocytic monocytic erythroleukemia chronic leukemia chronic myelocytic (granulocytic) leukemia chronic lymphocytic leukemia Polycythemia vera Lymphoma Hodgkin's disease non-Hodgkin's disease Multiple myeloma Waldenstrom's macroglobulinemia Heavy chain disease Solid tumors sarcomas and carcinomas fibrosarcoma myxosarcoma liposarcoma chondrosarcoma osteogenic sarcoma chordoma angiosarcoma endotheliosarcoma lymphangiosarcoma lymphangioendotheliosarcoma synovioma mesothelioma Ewing's tumor leiomyosarcoma rhabdomyosarcoma colon carcinoma pancreatic cancer breast cancer ovarian cancer prostate cancer squamous cell carcinoma basal cell carcinoma adenocarcinoma sweat gland carcinoma sebaceous gland carcinoma papillary carcinoma papillary adenocarcinomas cystadenocarcinoma medullary carcinoma bronchogenic carcinoma renal cell carcinoma hepatoma bile duct carcinoma choriocarcinoma seminoma embryonal carcinoma Wilms' tumor cervical cancer uterine cancer testicular tumor lung carcinoma small cell lung carcinoma bladder carcinoma epithelial carcinoma glioma astrocytoma medulloblastoma craniopharyngioma ependymoma pinealoma hemangioblastoma acoustic neuroma oligodendroglioma meningioma melanoma neuroblastoma retinoblastoma

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L9: Entry 1 of 17

File: USPT

Dec 31, 2002

DOCUMENT-IDENTIFIER: US 6500938 B1

TITLE: Composition for the detection of signaling pathway gene expression

DATE FILED (1):19980130Brief Summary Text (11):

In another aspect, the present invention encompasses an expression profile that can reflect the levels of a plurality of target polynucleotides in a sample. The expression profile comprises the microarray and a plurality of detectable complexes. Each detectable complex is formed by having at least one of the target polynucleotides hybridizing to at least one of the hybridizable array elements and further comprises a labeling moiety for detection. The expression profile of this invention is particularly useful in the diagnosis and the treatment of cancer, an immunopathology, a neuropathology and the like.

Brief Summary Text (29):

When the composition of the invention is employed as hybridizable array elements in a microarray, the array elements are organized in an ordered fashion so that each element is present at a specified location on the substrate. Because the array elements are at specified locations on the substrate, the hybridization patterns and intensities (which together create a unique expression profile) can be interpreted in terms of expression levels of particular genes and can be correlated with a particular disease or condition or treatment.

Detailed Description Text (71):

BRAITUT01 Library was constructed using 1 microgram of polyA RNA isolated from brain tumor tissue removed from a 50-year-old Caucasian female during a frontal lobectomy. Pathology indicated recurrent grade 3 oligoastrocytoma with focal necrosis and extensive calcification. Patient history included a speech disturbance and epilepsy. Patient medications included Tegretol (carbamazepine) as part of epilepsy therapy. The patient's brain had also been irradiated with a total dose of 5,082 cyg (Fraction 8). Family history included a brain tumor in a maternal uncle. cDNA synthesis was initiated using a NotI-oligo(dT) primer. Double-stranded cDNA was blunted, ligated to SalI adaptors, digested with NotI, size-selected, and cloned into the NotI and SalI sites of the pSPORT1 vector.

Detailed Description Text (72):

BRAITUT02 Library was constructed using 1 microgram of polyA RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. The patient presented with migraine headache. The patient developed a cerebral hemorrhage and pulmonary edema, and died during this hospitalization. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Previous surgeries included a nephroureterectomy. Patient medications included Decadron (dexamethasone) and Dilantin (phenytoin). Family history included a malignant neoplasm of the kidney in the father. cDNA synthesis was initiated using a NotI-oligo(dT) primer. Double-stranded cDNA was blunted, ligated to SalI adaptors, digested with NotI, size-selected, and cloned into the NotI and SalI sites of the pSPORT1 vector.

Detailed Description Text (73):

BRAITUT03 Library was constructed using 1 microgram of polyA RNA isolated from brain tumor tissue removed from the left frontal lobe of a 17-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated a grade 4 fibrillary giant

and small-cell astrocytoma. The patient presented with a headache and papilledema associated with increased intracranial pressure. Patient history included benign hypertension. Patient medications included Decadron (dexamethasone). Family history included benign hypertension and cerebrovascular disease in the grandparent(s). cDNA synthesis was initiated using a NotI-oligo(dT) primer. Double-stranded cDNA was blunted, ligated to SalI adaptors, digested with NotI, size-selected, and cloned into the NotI and SalI sites of the pSPORT1 vector.

Detailed Description Text (74):

BRAITUT07 Library was constructed using 0.8 micrograms of polyA RNA isolated from brain tumor tissue removed from the left frontal lobe of a 32-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated cerebral glioma of high-grade small-cell variant with metastases. The patient presented with nausea, vomiting, and headache. Patient history included arteriosclerotic coronary disease, alcohol and tobacco use, and marijuana use twice a week for six years. Family history included arteriosclerotic coronary disease in a grandparent. cDNA synthesis was initiated using a NotI-oligo(dT) primer. Double-stranded cDNA was blunted, ligated to EcoRI adaptors, digested with NotI, size-selected, and cloned into the NotI and EcoRI sites of the pINCY vector (Incyte).

Detailed Description Text (75):

BRAITUT08 Library was constructed using 1 microgram of polyA RNA isolated from brain tumor tissue removed from the left frontal lobe of a 47-year-old Caucasian male during excision of cerebral meningeal tissue. Pathology indicated grade 4 fibrillary astrocytoma with focal tumoral radionecrosis. The patient presented with paralysis and convulsive, intractable epilepsy. Patient history included cerebrovascular disease, deficiency anemia, hyperlipidemia, epilepsy, and tobacco use. Previous surgeries included tonsillectomy with adenoidectomy, repair of indirect inguinal hernia, and total arthroplasty in both knees. Patient medications included Tegretol (carbamazepine), Dilantin (phenytoin), dexamethasone, and multivitamins. Family history included cerebrovascular disease in a grandparent and a malignant prostate neoplasm in the father. cDNA synthesis was initiated using a NotI-oligo(dT) primer. Double-stranded cDNA was blunted, ligated to EcoRI adaptors, digested with NotI, size-selected, and cloned into the NotI and EcoRI sites of the pINCY vector (Incyte).

Detailed Description Text (76):

BRAITUT12 Library was constructed using 1 microgram of polyA RNA isolated from brain tumor tissue removed from the left frontal lobe of a 40-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated grade 4 gemistocytic astrocytoma. The patient presented with coma, epilepsy, and incontinence of urine and stool, Type II diabetes, and paralysis. Patient history included chronic nephritis and cesarean delivery. Patient medications included Decadron (dexamethasone) and phenytoin sodium. cDNA synthesis was initiated using a NotI-oligo(dT) primer. Double-stranded cDNA was blunted, ligated to EcoRI adaptors, digested with NotI, size-selected, and cloned into the NotI and EcoRI sites of the pINCY vector (Incyte).

Detailed Description Text (77):

BRAITUT13 Library was constructed using 1 microgram of polyA RNA isolated from brain tumor tissue removed from the left frontal lobe of a 68-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a meningioma in the left frontal lobe. The patient presented with depressive disorder, atrial fibrillation, and gait abnormality. Patient history included mitral stenosis with insufficiency and a tissue-graft replacement of an aortic valve. Patient medications included Coumadin (crystalline warfarin sodium), Zantac (ranitidine), bethametasone, Lasix (furosemide), and amiodarone. cDNA synthesis was initiated using a NotI-oligo(dT) primer. Double-stranded cDNA was blunted, ligated to EcoRI adaptors, digested with NotI, size-selected, and cloned into the NotI and EcoRI sites of the pINCY vector (Incyte).

Detailed Description Text (78):

BRAITUT22 Library was constructed using 0.5 micrograms of polyA RNA isolated from brain tumor tissue removed from the right frontal/parietal lobe of a 76-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated a meningioma. The patient presented with nonintractable epilepsy and transient limb paralysis. Patient history included benign hypertension, glaucoma, ventral hernia, tobacco use, and a normal delivery. Previous surgeries included an appendectomy, a total abdominal hysterectomy, a cholecystectomy, an intracapsular extraction of the lens, a hernia repair, and an open reduction of a fracture. The patient was not taking any medications. Family history included senile dementia in the father. cDNA synthesis was initiated using a NotI-oligo(dT) primer. Double-stranded cDNA was blunted, ligated

to EcoRI adaptors, digested with NotI, size-selected, and cloned into the NotI and EcoRI sites of the pINCY vector (Incyte).

Detailed Description Text (171):

LUNGTUT09 Library was constructed using 0.5 micrograms of polyA RNA isolated from lung tumor tissue removed from a 68-year-old Caucasian male during segmental lung resection. Pathology indicated invasive grade 3 squamous cell carcinoma in the right upper lobe, forming an infiltrating mass involving the bronchus and the surrounding parenchyma. The bronchial margin, bronchus intermedius, and proximal margin were negative for tumor. One (of 4) intrapulmonary peribronchial lymph nodes contained a metastatic tumor. An apical cap was identified. One (of 15) right paratracheal lower lymph nodes contained a metastatic tumor. Permanent superior mediastinal sections revealed metastatic squamous cell carcinoma in the lymph nodes. The patient presented with chest pain and pneumonia. Patient history included of Type II diabetes, thyroid disorder, depressive disorder, hyperlipidemia, esophageal ulcer, and tobacco and alcohol use. Patient medications included Glyburide for controlling blood glucose, Glucophage for controlling blood sugar, Synthroid (levothyroxine sodium, Propulsid, Cimetidine, Claritin, Prozac (fluoxetine hydrochloride), Ativan, and Vantin. Family history included alcohol use in the father, alcohol use and brain cancer in the mother, atherosclerotic coronary artery disease in the sibling(s), and atherosclerotic coronary artery disease in the grandparent(s). cDNA synthesis was initiated using a NotI-oligo(dT) primer. Double-stranded cDNA was blunted, ligated to EcoRI adaptors, digested with NotI, size-selected, and cloned into the NotI and EcoRI sites of the pINCY vector (Incyte).

Detailed Description Paragraph Table (4):

[Norway rat.] SEQ ID NO: 320 1854243 2039275 males-absent on the first. [fruit fly.] SEQ ID NO: 321 1854478 156418 putative. [Caenorhabditis elegans.] SEQ ID NO: 322 1859317 1161099 Mus musculus (clone HIC-53) hydrogen peroxide-inducible protein [Mus musculus (clone: HIC-53) embryo calvariagag cDNA to mRNA.] SEQ ID NO: 323 1870882 487418 actin filament-associated protein. [chicken.] SEQ ID NO: 324 1872615 35014 Human melanoma mRNA for nck protein, showing homology to src. [human.] SEQ ID NO: 325 1880501 395085 ATP receptor P2Y1. [chicken.] SEQ ID NO: 326 1881130 1763665 Snk interacting protein 2-28. [human.] SEQ ID NO: 327 1888801 206809 Rat pot. G protein coupled receptor (RTA) mRNA, complete cds. [Rat (strain Sprague Dawley) adult thoracic aorta, cDNA to mRNA,] SEQ ID NO: 328 189981 1526977 H. sapiens mRNA for ryanodine receptor 2. [human.] SEQ ID NO: 329 1907628 1888565 Mus musculus protein phosphatase 1 binding protein PTG mRNA, [house mouse.] SEQ ID NO: 330 1909132 307158 mas protein. [human.] SEQ ID NO: 331 1911587 1220173 dual specificity phosphatase. [Norway rat.] SEQ ID NO: 332 1913754 164763 dihydropyridine-sensitive calcium channel alpha-2 subunit. [European rabbit.] SEQ ID NO: 333 1916151 1524004 serine/threonine protein kinase. [fruit fly.] SEQ ID NO: 334 1917286 1842087 Human tyrosine phosphatase-like protein homolog hSTYXb mRNA, [human.] SEQ ID NO: 335 1920752 1514568 canalicular multidrug resistance protein. [human.] SEQ ID NO: 336 193629 763534 secretin receptor [Homo sapiens] SEQ ID NO: 337 194510 340478 DNA-binding protein. [human.] SEQ ID NO: 338 195647 642800 PP2C [Paramecium tetraurelia] SEQ ID NO: 339 1961860 1747370 H. sapiens mRNA for putative GABA-gated chloride channel. [human.] SEQ ID NO: 340 1963281 595421 protein kinase. [house mouse.] SEQ ID NO: 341 1963772 508233 Rcalp. [baker's yeast.] SEQ ID NO: 342 196640 505548 zinc-finger protein (ZNFpT7). [human.] SEQ ID NO: 343 1966404 2108051 Human cGMP-stimulated 3',5'-cyclic nucleotide phosphodiesterase [human.] SEQ ID NO: 344 1971037 181949 endothelial differentiation protein (edg-1). [human.] SEQ ID NO: 345 1973931 1407587 MEK Kinase 3. [house mouse.] SEQ ID NO: 346 197500 454324 H. sapiens ZNF81 gene. [human.] SEQ ID NO: 347 1989157 387675 protocadherin 42. [human.] SEQ ID NO: 348 1989493 178437 Human phosphatase 2A mRNA, partial cds. [human.] SEQ ID NO: 349 1989936 180686 Human 2',3'-cyclic nucleotide 3'-phosphodiesterase mRNA, complete [Human glioma (cell line U-251MG), cDNA to mRNA.] SEQ ID NO: 350 1992818 1806048 nuclear DNA helicase II. [human.] SEQ ID NO: 351 1992915 1941925 retinal epithelial membrane protein. [chicken.] SEQ ID NO: 352 1994216 387675 protocadherin 42. [human.] SEQ ID NO: 353 1996651 1054887 novel transcript; similar to transcription factors activation [human.] SEQ ID NO: 354 1998162 190459 Human endomembrane proton pump subunit mRNA, complete cds. [Human kidney, cDNA to mRNA.] SEQ ID NO: 355 2011686 1597729 serine threonine kinase. [house mouse.] SEQ ID NO: 356 2012970 20756 RAS-related GTP-binding protein. [pea.] SEQ ID NO: 357 2017571 1550782 M. musculus mRNA for transcription factor BARX1. [house mouse.] SEQ ID NO: 358 2018356 1656001 rit. [human.] SEQ ID NO: 359 2018536 1504145 growth hormone secretagogue receptor type 1a. [pig.] SEQ ID NO: 360 2023607 558349 host cell factor. [human.] SEQ ID NO: 361 2024210 212485 ovoinhibitor. [chicken.] SEQ ID NO: 362 2028257 307184 Homo sapiens ERK activator kinase (MEK2) mRNA. [Homo sapiens cDNA to mRNA.] SEQ ID NO: 363 2029134 517365 R. norvegicus olp4 mRNA. [Norway rat.] SEQ ID NO: 364 2039628 205038 Rattus norvegicus K+ channel mRNA, sequence. [Rattus norvegicus adult brain cDNA to

mRNA.] SEQ ID NO: 365 2047048 1809219 human K⁺ channel beta 2 subunit mRNA, complete cds. [human.] SEQ ID NO: 366 2049369 207464 transferrin receptor. [Norway rat.] SEQ ID NO: 367 2054141 1397246 coded for by *C. elegans* cDNA yk112f3.5; coded for by *C. elegans* [Caenorhabditis elegans.] SEQ ID NO: 368 2054814 192644 Mouse connexin 31.1 (Cx31.1) gene, complete cds, 8 clone. [Mus musculus (strain GR) (library: charon 4A of B. Groner) adult] SEQ ID NO: 369 2055179 474283 Mus musculus BALB/c zinc-finger protein Blimp-1 mRNA, complete cds. [house mouse.] SEQ ID NO: 370 2055790 1399804 Human Bcl2, p53 binding protein Bbp/53BP2 (BBP/53BP2) mRNA, [human.] SEQ ID NO: 371 2056018 1403708 Rattus norvegicus furosemide-sensitive K-Cl cotransporter (KCC2) [Norway rat.] SEQ ID NO: 372 2059915 541667 musashi. [fruit fly.] SEQ ID NO: 373 2060327 263673 FlFo-ATPase subunit e [mice, Balb/c, Peptide, 71 aa]. [Mus sp. Balb/c.] SEQ ID NO: 374 2060769 212659 skeletal muscle C-protein. [chicken.] SEQ ID NO: 375 2061942 807817 putative RNA helicase HRH1 [Homo sapiens] SEQ ID NO: 376 2062218 806296 prIL-16 = putative interleukin-16 precursor [Homo sapiens] SEQ ID NO: 377 2069502 171114 ATPase. [baker's yeast.] SEQ ID NO: 378 2077640 1906041 Human embryonic ectoderm development protein homolog (eed) mRNA, [human.] SEQ ID NO: 379 2079292 439260 T26G10.1. [Caenorhabditis elegans.] SEQ ID NO: 380 2080608 1504088 DNA-binding protein. [house mouse.] SEQ ID NO: 381 2081193 220418 glutamate receptor channel subunit delta-1. [house mouse.] SEQ ID NO: 382 2081690 1857160 Human zinc finger transcription factor hEZF (EZF) mRNA, complete [human.] SEQ ID NO: 383 2087413 606948 neuron-restrictive silencer factor. [human.] SEQ ID NO: 384 2088215 1669383 Human BAC clone RG067M09 7 from-7q22, complete sequence. [human.] SEQ ID NO: 385 2096740 2062691 Human sodium phosphate transporter (NPT4) mRNA, complete cds. [human.] SEQ ID NO: 386 2098429 1381810 skeletal muscle LIM-protein SLIM2. [human.] SEQ ID NO: 387 2102405 348238 Human mRNA, complete cds. [Homo sapiens cDNA to mRNA.] SEQ ID NO: 388 2102713 1840052 Human liver GABA transport protein mRNA, 3' end. [human.] SEQ ID NO: 389 2106395 289622 homology with ATP-dependent RNA helicase; putative. [Caenorhabditis elegans.] SEQ ID NO: 390 2108581 944911 inositol polyphosphate 4-phosphatase [Homo sapiens] SEQ ID NO: 391 2108752 1507672 GS3955. [human.] SEQ ID NO: 392 2109526 1628399 inter-alpha-trypsin inhibitor heavy chain H3. [human.] SEQ ID NO: 393 2109849 531750 probable mitochondrial protein. [baker's yeast.] SEQ ID NO: 394 2110163 1418484 C54G4.1. [Caenorhabditis elegans.] SEQ ID NO: 395 2110277 4178 PIF gene product (AA 1-857). [baker's yeast.] SEQ ID NO: 396 2111542 2062399 calcium calmodulin dependent kinase CPG16. [Norway rat.] SEQ ID NO: 397 2113436 1508828 Human seven in absentia homolog mRNA, complete cds. [human.] SEQ ID NO: 398 2114703 525195 *C. griseus* epsilon-COP mRNA. [Chinese hamster.] SEQ ID NO: 399 2114943 193979 Hox-3.1 protein. [house mouse.] SEQ ID NO: 400 2117559 289614 homology with glucose induced repressor, GRR1; putative. [Caenorhabditis elegans.] SEQ ID NO: 401 2118071 450553 ORF YKR413. [baker's yeast.] SEQ ID NO: 402 2121021 625041 basic domain/leucine zipper transcription factor [Mus musculus] SEQ ID NO: 403 2121175 1065718 tenascin-C. [zebrafish.] SEQ ID NO: 404 2121278 217399 limulus factor C precursor. [Japanese horseshoe crab.] SEQ ID NO: 405 2121285 54257 Mouse mRNA for talin. [house mouse.] SEQ ID NO: 406 2121593 924921 branched-chain alpha-ketoacid dehydrogenase kinase [Rattus norvegicus] SEQ ID NO: 407 2122108 55818 Rat mRNA for beta COP. [Norway rat.] SEQ ID NO: 408 2122627 1568629 Mus musculus nuclear LIM interactor (NLI) mRNA, complete cds. [house mouse.] SEQ ID NO: 409 2123679 206130 cyclic nucleotide phosphodiesterase. [Norway rat.] SEQ ID NO: 410 2124153 1929896 Human stat-like protein (Fe65) mRNA, complete cds. [human.] SEQ ID NO: 411 2124608 1881851 SOX5 = Sry-related HMG box gene {alternatively spliced} [human, [human testis.] SEQ ID NO: 412 2125658 182923 gamma-aminobutyric acid receptor beta-1 subunit. [human.] SEQ ID NO: 413 2132279 1262435 put. 26S protease subunit. [pig.] SEQ ID NO: 414 2132361 179412 DNA-binding factor. [human.] SEQ ID NO: 415 2137141 2182130 G protein beta 5 subunit. [Norway rat.] SEQ ID NO: 416 2137420 173142 zinc finger protein. [baker's yeast.] SEQ ID NO: 417 2137838 1914169 F23B2.4. [Caenorhabditis elegans.] SEQ ID NO: 418 2148792 1373393 Human zinc finger protein (LD5-1) mRNA, complete cds. [human.] SEQ ID NO: 419 214915 2181950 stress-activated protein kinase-3. [house mouse.] SEQ ID NO: 420 2150261 914027 neurotransmitter transporter rB21a [rat] SEQ ID NO: 421 2150668 202861 Rat alternatively spliced mRNA. [Rattus norvegicus (strain Sprague-Dawley) male stomach and testis] SEQ ID NO: 422 2153874 802104 PP1M M110 = protein phosphatase [rat] SEQ ID NO: 423 2155287 881961 NEX-1 [Mus musculus] SEQ ID NO: 424 2155484 2058550 Human leukemogenic homolog protein (MEIS1) mRNA, complete cds. [human.] SEQ ID NO: 425 215793 1613851 Human zinc finger protein zfp2 (zf2) mRNA, partial cds. [human.] SEQ ID NO: 426 215814 263348 zinc finger = ZNF126 [human, Peptide